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Search Results -

Terms	Documents
sonif$ adj3 (solvent adj2 remov$)	7

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L2	sonif$ adj3 (solvent adj2 remov$)	7	L2
L1	ultrasonif$ adj3 (solvent adj2 remov$)	0	L1

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Search Results -

Terms	Documents
sonic$ adj5 (solvent adj2 remov$)	63

Database:
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Search: L4

Refine Search | Recall Text | Clear | Interrupt

Search History

DATE: Wednesday, May 30, 2007 **Purge Queries** Printable Copy Create Case

Set Name side by side	Query	Hit Count	Set Name result set
DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L4	sonic$ adj5 (solvent adj2 remov$)	63	L4
L3	sonif$ adj5 (solvent adj2 remov$)	10	L3
L2	sonif$ adj3 (solvent adj2 remov$)	7	L2
L1	ultrasonif$ adj3 (solvent adj2 remov$)	0	L1

END OF SEARCH HISTORY

№ 388 536 EXPOSÉ D'INVENTION № 388 536

CONFÉDÉRATION SUISSE

BUREAU FÉDÉRAL DE LA PROPRIÉTÉ INTELLECTUELLE

Classification : 30 i, 3
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Brevet délivré le 28 février 1965

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R

BREVET PRINCIPAL

Pierre André Pottier, Paris (France)

Procédé de protection des lipides contre l'oxydation

Pierre André Pottier, Paris (France), est mentionné comme étant l'inventeur

Il est bien connu que beaucoup de lipides contiennent des esters non saturés et qu'en conséquence ils s'altèrent plus ou moins rapidement par autooxydation. On a tenté d'éviter ces altérations en mélangeant aux lipides altérables des anti-oxygène et plus spécialement de l'acide ascorbique seul ou de l'acide citrique seul, mais ces acides présentent des inconvénients.

D'une part, l'acide ascorbique n'est pas soluble dans les lipides et l'acide citrique l'est très peu ; il est donc fort malaisé de réaliser une répartition homogène de ces acides dans le lipide à traiter. D'autre part, le pouvoir anti-oxygène de ces composés n'est que moyen, ce qui conduit à en employer des proportions relativement élevées.

La présente invention a pour objet un procédé de protection des lipides contre l'oxydation, caractérisé par le fait de répartir dans la masse du lipide à protéger un mélange d'acide ascorbique et d'acide citrique.

Selon un mode d'exécution avantageux de ce procédé, on procède d'abord au mélange de l'acide ascorbique et de l'acide citrique avec un acide gras ou un ester d'acide gras, et c'est ce mélange qui est incorporé à la masse du lipide à protéger.

Le procédé qui vient d'être défini est avantageusement réalisé de la manière suivante : chacun des acides ascorbique et citrique est tout d'abord mélangé à une fraction d'un acide gras ou d'un ester d'acide gras, puis les deux mélanges sont réunis après fusion de chacun des mélanges partiels, et c'est le produit ainsi obtenu qui est ensuite introduit dans le lipide à protéger.

Le titulaire a en effet constaté le fait surprenant que l'acide ascorbique et l'acide citrique agissent en synergie, c'est-à-dire que leur mélange produit un effet anti-oxygène de beaucoup plus élevé que la somme des effets de chacun de ces corps pris isolément.

Chacun de ces acides ascorbique et citrique peut entrer dans le mélange qui vient d'être défini (mélange des deux acides et d'un acide gras ou d'un ester d'acide gras) dans une proportion qui peut aller, environ, de 1 à 18 % en poids dudit mélange.

Pour la mise en œuvre de l'invention, on peut utiliser un acide gras quelconque et notamment acide stéarique, palmitique, laurique, oléique, linoléique, etc., soit tel, soit estérifié à l'aide d'un polyalcool également quelconque, par exemple l'un des polyalcools suivants : glycérol, glycols (éthylénique, propylénique, diéthylénique, triéthylénique, polyoxyéthylénique). En ce qui concerne les acides gras non saturés, on donnera la préférence à leurs esters glycéroliques et glycoliques.

Dans un mode de réalisation avantageux de cette invention, on utilise de préférence l'acide palmitique ou stéarique, soit pur, soit sous forme du mono- di- ou tri- ester de glycérol.

On peut également utiliser soit un mélange d'acides gras, soit un mélange d'esters de ces mêmes acides.

La préparation dudit mélange peut s'effectuer en présence d'un solvant alcoolique qui peut être soit un monoalcool de bas poids moléculaire, tel l'éthanol, le propanol, le butanol, etc., soit un diol pur ou monoestérifié tel que l'éthanediol, le propanediol, le butanediol, etc.

Les exemples suivants illustrent l'invention.

Dans ces exemples, les parties indiquées sont des parties en poids.

Exemple 1

Pour préparer le mélange contenant l'acide citrique et l'acide ascorbique on utilise les matières premières suivantes :

	Parties
Acide ascorbique	1
Acide citrique	14
Ethanol	11
Acide stéarique ou stéarate de glycérol	85

Dans une partie de l'éthanol, dont le titre peut être compris entre 60 et 65°, on fait dissoudre à chaud l'acide ascorbique tout en agitant ; après dissolution complète, on incorpore une fraction de l'acide stéarique ou du stéarate. On maintient le mélange sous agitation vive à une température qui ne doit pas dépasser 70°, jusqu'à évaporation aussi poussée que possible du solvant. On coule ensuite dans un moule conique, on laisse décanter et prendre en masse par refroidissement. On démoule le pain, on rejette les produits résiduaires de décantation qui se trouvent au fond du récipient et on lave le pain pour le débarrasser de la fraction de ces produits qui peuvent y adhérer.

Dans le reste de l'éthanol, on dissout l'acide citrique et l'on opère de la manière qui vient d'être décrite après avoir également incorporé le reste de l'acide stéarique ou du stéarate.

On obtient ainsi deux produits partiels que l'on fait fondre et que l'on mélange, puis le produit final ainsi préparé est coulé en pains et éventuellement râpé. De manière connue, on répartit uniformément le mélange ainsi préparé dans le lipide à protéger. La dose de produit est comprise entre 0,03 et 0,08 g pour 100 g de lipide.

Exemple 2

En utilisant le mode opératoire de l'exemple 1, on prépare un mélange à partir de :

	Parties
Acide ascorbique	14
Acide citrique	1
Butanol	11
Acide stéarique ou stéarate de glycérol	85

Exemple 3

Pour la réalisation du mélange, on part de :

	Parties
Acide ascorbique	3
Acide citrique	12
Propanol	3
Acide palmitique	25
Monostéarate de glycérol	60

Dans cet exemple, on dissout l'acide ascorbique dans le propanol alors que l'acide citrique est séparément dissous dans l'acide palmitique. Cette variante mise à part, on opère de la manière décrite dans l'exemple 1.

Exemple 4

Pour la préparation d'un mélange on part de :

	Parties
Butanediol	20
Acide ascorbique	2
Acide citrique	11
Palmitate de stéaryle	67

Le butanediol est tout d'abord porté à une température comprise entre 130° et 140° C environ. On introduit par petites fractions et sous agitation vive l'acide ascorbique. Après dissolution complète, on ajoute l'acide citrique qu'on laisse dissoudre également, puis on laisse tomber la température vers 80° et on ajoute l'acide gras ou son ester fondu à l'avance. On maintient l'agitation vive 30 minutes environ. On coule dans un récipient dans lequel un excès de solvant se sépare de la masse. Après solidification de la phase grasse, on démoule et on lave le pain obtenu pour le débarrasser des traces de solvant et des produits résiduaires qui peuvent y adhérer.

Exemple 5

On part des produits suivants :

	Parties
Ethanediol	5
Acide ascorbique	1
Acide palmitique	28
Acide citrique	14
Stéarate de stéaryle	52

et l'on opère de la manière décrite dans l'exemple 4.

L'expérience montre que le mélange ainsi obtenu est actif à des doses extrêmement faibles puisque son seuil d'activité se trouve à 0,03 pour cent du lipide à protéger.

Quelle que soit la manière dont il est préparé, le mélange d'acides citrique et ascorbique est uniformément réparti dans le lipide à protéger ; la dose du mélange utilisée est, dans le cas général, comprise entre 0,03 g et 0,08 g pour 100 g de lipide.

En particulier, on utilise avantageusement la méthode qui consiste à mélanger la quantité totale de ce mélange avec une partie, par exemple le quart, du lipide à protéger. On répartit ensuite le mélange ainsi obtenu avec la fraction restante du lipide à protéger.

REVENDICATION

Procédé pour la protection des lipides contre l'oxydation, caractérisé par le fait de répartir dans la masse du lipide à protéger un mélange d'acide ascorbique et d'acide citrique.

SOUS-REVENDICATIONS

1. Procédé selon la revendication, dans lequel l'acide ascorbique et l'acide citrique sont mélangés à un acide gras ou un ester d'acide gras avant leur incorporation au lipide.

2. Procédé selon la revendication et la sous-revendication 1, selon lequel on utilise une proportion d'acide ascorbique et citrique allant, pour chacun d'entre eux, de 1 à 18 % en poids du mélange constitué par ces acides et l'acide gras ou l'ester d'acide gras.

3. Procédé selon la sous-revendication 1, caractérisé en ce que l'ester d'acide gras est un ester de polyalcool.

Pierre André Pottier
Mandataire : R. Rottmann, ing. dipl., Zurich

L2: Entry 13 of 139 File: PGPB Dec 14, 2006

DOCUMENT-IDENTIFIER: US 20060280430 A1
TITLE: Method for delivering particulate drugs to tissues

Abstract Paragraph:
The present invention is concerned with delivering a pharmaceutical composition to a tissue target of a mammalian subject for treating brain diseases or disorders. The process includes the steps of: (i) providing a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns, and (ii) administering the dispersion to the mammalian subject for delivery to the tissue target of a portion of the pharmaceutical composition by cells capable of reaching the tissue target. The dispersion of the pharmaceutical composition as particles, for example, can be phagocytised or adsorbed by the cells prior or subsequent to administration into the mammalian subject. The dispersion of the pharmaceutical composition can be administered to the central nervous system or the vascular system. After administration, the loaded cells transport the pharmaceutical composition as particles into the tissue target.

Brief Summary Text:
[0007] Many therapeutic or diagnostic agents are poorly soluble or insoluble in aqueous solutions. Such drugs provide challenges to delivering them orally or parenterally. Compounds that are insoluble in water can have significant benefits when formulated as a stable suspension of sub-micron particles. Accurate control of particle size is essential for safe and efficacious use of these formulations. Particles must be less than seven microns in diameter to safely pass through capillaries without causing emboli (Allen et al., 1987; Davis and Taube, 1978; Schroeder et al., 1978; Yokel et al., 1981). One solution to this problem is the production of small particles of the insoluble drug candidate and the creation of a microparticulate or nanoparticulate suspension. In this way, drugs that were previously unable to be formulated in an aqueous system can be made suitable for intravenous administration. Suitability for intravenous administration includes small particle size (<7 .mu.m), low toxicity (as from toxic formulation components or residual solvents), and bioavailability of the drug particles after administration.

Brief Summary Text:
[0008] Bender et al. disclose the treatment of HIV-infected monocytes/macrophages with polyhexylcyanoacrylate nanoparticles loaded with either the nucleoside analog zalcitabine (2',3'-dideoxycytidine), or saquinavir, a protease inhibitor (Bender et al., Efficiency of Nanoparticles as a Carrier System for Antiviral Agents in Human Immunodeficiency Virus-Infected Human Monocytes/Macrophases In Vitro, Antimicrobial Agents and Chemotherapy, June 1996, volume 40(6), p. 1467-1471). The polyhexylcyanoacrylate nanoparticles were prepared by emulsion polymerization and tested in-vitro for antiviral activity in primary human monocytes/macrophages. An aqueous solution of saquinavir showed little antiviral activity in HIV-infected macrophages, whereas the nanoparticulate formulation demonstrated significant antiviral activity at one-tenth the solution concentration. At a concentration of 100 nM, saquinavir in solution was completely inactive in chronically HIV-infected macrophages, but when bound to nanoparticles it caused a 35% decrease in viral antigen production. In this study, the drug was entrained in a polymer (polyhexylcyanoacrylate) matrix. The idea of preparing pure, solid drug

nanoparticles for delivery to macrophages was not disclosed. Particles were only delivered to macrophages in-vitro and did not contemplate drug delivery by administering nanoparticle-treated cells that are capable of reaching the brain to transport the drug. Von Briesen discloses the phagocytozation of nanoparticles of entrained in polymers (e.g., polyhexylcyanoacrylate) by monocytes/macrophages (H. von Briesen, Controled Release of Antiretroviral Drugs, AIDS Rev, 2000, volume 2, pages 31-38.

Brief Summary Text:
[0011] The present invention provides a method for delivering a pharmaceutical composition to the tissues of a mammalian subject by cellular transport. In a preferred embodiment, the process includes the steps of: (i) isolating cells from the mammalian subject, (ii) contacting the cells with a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns, (iii) allowing sufficient time for cell intracellular uptake of the particles, and (iv) administering to the mammalian subject the loaded cells to deliver a portion of the pharmaceutical composition to the tissues. There are numerous types of cells in the mammalian subject that are capable of this type of cellular uptake and transport of particles. These cells include, but are not limited to, macrophages, monocytes, granulocytes, neutrophils, basophils, and eosinophils.

Brief Summary Text:
[0012] After isolation from the mammalian subject, the cells in contact with the dispersion of the pharmaceutical composition as particles may take up the particles through phagocytosis or adsorption of the particle onto the surface of the cell. In a preferred form of the invention, during contact with the cells, the particles are at a concentration higher than the thermodynamic saturation solubility thereby allowing the particles to remain in particulate form during uptake and delivery to the tissue target by the cells.

Brief Summary Text:
[0014] In another preferred embodiment, the method comprises the steps of providing a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns and administering the dispersion directly to the mammalian subject for delivery to the tissue target of a portion of the pharmaceutical composition by cells capable of reaching the tissue target. In-vivo cell intracellular uptake occurs within the lymphatic system or vascular system of the mammalian subject.

Brief Summary Text:
[0018] The present invention also provides a pharmaceutical composition for delivery to the tissue target comprising a dispersion of the pharmaceutical composition provided as particles having an average particle size of from about 150 nm to about 100 microns and adapted for administering to a mammalian subject for delivery to the brain of an effective amount of the pharmaceutical composition by cells capable of reaching the tissue target.

Brief Summary Text:
[0020] As a particulate, the drug is taken up by macrophages which afford sanctuaries to viral and bacterial diseases such as the human immunodeficiency virus (HIV). Because the drug is concentrated in the macrophages, the infecting organism is exposed to much larger amounts of the drug thereby killing the organism. Macrophages can pass through numerous tissues including, but not limited to, the cerebrospinal fluid-brain barrier into the brain and release concentrations of the drug in the brain due to dissolution of the particle within the macrophages. As a result, free viral and bacterial organisms residing in the brain are exposed to the drug at concentrations higher than what is typically feasible through oral administration. The brain is able to rapidly clear microbial organisms, thus preventing the emergence of drug-resistant organisms. Furthermore, the subsequent

seeding and perpetuation within the body of the disease-causing organism within the body can be mitigated. Administering the drug in this manner allows increased drug utilization within the brain while permitting use of lower drug levels. Excessive liver metabolism of drugs can be avoided and the cost of therapy can be reduced through this invention.

Description of Disclosure:
[0027] Diagnostic agents include the x-ray imaging agents and contrast media. Examples of x-ray imaging agents include WIN-8883 (ethyl 3,5-diacetamido-2,4,6-triiodobenzoate) also known as the ethyl ester of diatrazoic acid (EEDA), WIN 67722, i.e., (6-ethoxy-6-oxohexyl-3,5-bis(acetamido)-2,4,6-triiodobenzoate; ethyl-2-(3,5-bis(acetamido)-2,4,6-triiodo-benzoyloxy)butyrate (WIN 16318); ethyl diatrizoxyacetate (WIN 12901); ethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy) propionate (WIN 16923); N-ethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy acetamide (WIN 65312); isopropyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy) acetamide (WIN 12855); diethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy malonate (WIN 67721); ethyl 2-(3,5-bis(acetamido)-2,4,6-triiodobenzoyloxy) phenylacetate (WIN 67585); propanedioic acid, [[3,5-bis(acetylamino)-2,4,5-triodobenzoyl]oxy]bis(1-methyl)ester (WIN 68165); and benzoic acid, 3,5-bis (acetylamino)-2,4,6-triodo-4-(ethyl-3-ethoxy-2-butenoate)ester (WIN 68209). Preferred contrast agents include those that are expected to disintegrate relatively rapidly under physiological conditions, thus minimizing any particle associated inflammatory response. Disintegration may result from enzymatic hydrolysis, solubilization of carboxylic acids at physiological pH, or other mechanisms. Thus, poorly soluble iodinated carboxylic acids such as iodipamide, diatrizoic acid, and metrizoic acid, along with hydrolytically labile iodinated species such as WIN 67721, WIN 12901, WIN 68165, and WIN 68209 or others may be preferred.

Description of Disclosure:
[0032] The dispersion of the pharmaceutical composition can be sterilized prior to administering. Sterilization can be performed by any medical sterilization process including heat sterilization or sterilization by gamma irradiation. It can also be sterilized by filtration, either directly as a dispersion having particle sizes under 200 nm, or by sterile filtration of the solutions used in the precipitation process, prior to forming the solid dispersion. Sterilization can also be accomplished by brief application of very high pressure (greater than 2000 atmospheres), or by a combination of high pressure and elevated temperature.

Description of Disclosure:
[0034] The particles utilized in the present invention have an average effective particle size of generally from about 150 nm to about 100 .mu.m as measured by dynamic light scattering methods (e.g., photocorrelation spectroscopy, laser diffraction, low-angle laser light scattering (LALLS), medium-angle laser light scattering (MALLS)), light obscuration methods (Coulter method, for example), rheology, or microscopy (light or electron). The preferred average effective particle size depends on factors such as the intended route of administration, formulation, solubility, toxicity and bioavailability of the compound.

Description of Disclosure:
[0035] The processes for preparing the particles used in the present invention can be accomplished through numerous techniques known to those skilled in the art. A representative, but non-exhaustive, discussion of techniques for preparing particle dispersions of pharmaceutical compositions follows.

Description of Disclosure:
I. Energy Addition Techniques for Forming Small Particle Dispersions

Description of Disclosure:
[0036] In general, the method of preparing small particle dispersions using energy

addition techniques includes the step of adding the pharmaceutically active compound, which sometimes shall be referred to as a drug, in bulk form to a suitable vehicle such as water or aqueous solution containing one or more of the surfactants set forth below, or other liquid in which the pharmaceutical compound is not appreciably soluble, to form a first suspension, which shall be referred to as a presuspension. Energy is added to the presuspension to form a particle dispersion which is physically more stable than the presuspension. Energy is added by mechanical grinding (e.g., pearl milling, ball milling, hammer milling, fluid energy milling, jet milling, or wet grinding). Such techniques are disclosed in U.S. Pat. No. 5,145,684, which is incorporated herein by reference and made a part hereof.

Description of Disclosure:
[0039] Regardless of the energy addition technique used, the dispersion of small particles must be sterilized prior to use. Sterilization can be accomplished by heat sterilization, gamma irradiation, filtration (either directly as a dispersion having particle sizes under 200 nm, or by sterile filtration of the solutions used in the precipitation process, prior to forming the solid dispersion), and by application of very high pressure (greater than 2000 atmospheres), or by a combination of high pressure and elevated temperature.

Description of Disclosure:
II. Precipitation Methods for Preparing Submicron Sized Particle Dispersions

Description of Disclosure:
[0040] Small particle dispersions can also be prepared by precipitation techniques. The following is a description of examples of precipitation techniques.

Description of Disclosure:
[0043] One suitable emulsion precipitation technique is disclosed in the co-pending and commonly assigned U.S. Ser. No. 09/964,273, which is incorporated herein by reference and is made a part hereof. In this approach, the process includes the steps of: (1) providing a multiphase system having an organic phase and an aqueous phase, the organic phase having a pharmaceutically active compound therein; and (2) sonicating the system to evaporate a portion of the organic phase to cause precipitation of the compound in the aqueous phase to form a dispersion of small particles. The step of providing a multiphase system includes the steps of: (1) mixing a water immiscible solvent with the pharmaceutically active compound to define an organic solution, (2) preparing an aqueous based solution with one or more surface active compounds, and (3) mixing the organic solution with the aqueous solution to form the multiphase system. The step of mixing the organic phase and the aqueous phase can include the use of piston gap homogenizers, colloidal mills, high speed stirring equipment, extrusion equipment, manual agitation or shaking equipment, microfluidizer, or other equipment or techniques for providing high shear conditions. The crude emulsion will have oil droplets in the water of a size of approximately less than 1 .mu.m in diameter. The crude emulsion is sonicated to define a microemulsion and eventually to provide a dispersion of small particles.

Description of Disclosure:
[0046] Small particle dispersions can also be prepared using solvent anti-solvent precipitation technique disclosed by Fessi et al. in U.S. Pat. No. 5,118,528 and by Leclef et al. in U.S. Pat. No. 5,100,591 which are incorporated herein by reference and made a part hereof. Both processes include the steps of: (1) preparing a liquid phase of a biologically active substance in a solvent or a mixture of solvents to which may be added one or more surfactants; (2) preparing a second liquid phase of a non-solvent or a mixture of non-solvents, the non-solvent is miscible with the solvent or mixture of solvents for the substance; (3) adding together the solutions of (1) and (2) with stirring; and (4) removing of unwanted solvents to produce a dispersion of small particles. These methods are distinguished from those described under the above section, "Microprecipitation Methods", in that they do not provide

for a last step of adding energy to the suspension in the form of high-shear mixing or heat.

Description of Disclosure:
[0047] Small particle dispersions can be formed using phase inversion precipitation as disclosed in U.S. Pat. Nos. 6,235,224, 6,143,211 and U.S. Patent Application No. 2001/0042932, each of which is incorporated herein by reference and made a part hereof. Phase inversion is a term used to describe the physical phenomena by which a polymer dissolved in a continuous phase solvent system inverts into a solid macromolecular network in which the polymer is the continuous phase. One method to induce phase inversion is by the addition of a nonsolvent to the continuous phase. The polymer undergoes a transition from a single phase to an unstable two phase mixture: polymer rich and polymer poor fractions. Micellar droplets of nonsolvent in the polymer rich phase serve as nucleation sites and become coated with polymer. The '224 patent discloses that phase inversion of polymer solutions under certain conditions can bring about spontaneous formation of discrete microparticles, including nanoparticles. The '224 patent discloses dissolving or dispersing a polymer in a solvent. A pharmaceutical agent is also dissolved or dispersed in the solvent. For the crystal seeding step to be effective in this process it is desirable the agent is dissolved in the solvent. The polymer, the agent and the solvent together form a mixture having a continuous phase, wherein the solvent is the continuous phase. The mixture is then introduced into at least tenfold excess of a miscible nonsolvent to cause the spontaneous formation of the microencapsulated microparticles of the agent having an average particle size of between 10 nm and 10 .mu.m. The particle size is influenced by the solvent:nonsolvent volume ratio, polymer concentration, the viscosity of the polymer-solvent solution, the molecular weight of the polymer, and the characteristics of the solvent-nonsolvent pair.

Description of Disclosure:
[0048] Small particle dispersions can be formed by pH shift precipitation techniques. Such techniques typically include a step of dissolving a drug in a solution having a pH where the drug is soluble, followed by the step of changing the pH to a point where the drug is no-longer soluble. The pH can be acidic or basic, depending on the particular pharmaceutical compound. The solution is then neutralized to form a dispersion of small particles. One suitable pH shifting precipitation process is disclosed in U.S. Pat. No. 5,665,331, which is incorporated herein by reference and made a part hereof. The process includes the step of dissolving of the pharmaceutical agent together with a crystal growth modifier (CGM) in an alkaline solution and then neutralizing the solution with an acid in the presence of suitable surface-modifying surface-active agent or agents to form a small particle dispersion of the pharmaceutical agent. The precipitation step can be followed by steps of diafiltration clean-up of the dispersion and then adjusting the concentration of the dispersion to a desired level.

Description of Disclosure:
[0050] Suitable infusion precipitation techniques to form small particle dispersions are disclosed in the U.S. Pat. Nos. 4,997,454 and 4,826,689, which are incorporated herein by reference and made a part hereof. First, a suitable solid compound is dissolved in a suitable organic solvent to form a solvent mixture. Then, a precipitating nonsolvent miscible with the organic solvent is infused into the solvent mixture at a temperature between about -10.degree. C. and about 100.degree. C. and at an infusion rate of from about 0.01 ml per minute to about 1000 ml per minute per volume of 50 ml to produce a suspension of precipitated non-aggregated solid particles of the compound with a substantially uniform mean diameter of less than 10 .mu.m. Agitation (e.g., by stirring) of the solution being infused with the precipitating nonsolvent is preferred. The nonsolvent may contain a surfactant to stabilize the particles against aggregation. The particles are then separated from the solvent. Depending on the solid compound and the desired particle size, the parameters of temperature, ratio of nonsolvent to solvent,

infusion rate, stir rate, and volume can be varied according to the invention. The particle size is proportional to the ratio of nonsolvent:solvent volumes and the temperature of infusion and is inversely proportional to the infusion rate and the stirring rate. The precipitating nonsolvent may be aqueous or non-aqueous, depending upon the relative solubility of the compound and the desired suspending vehicle.

Description of Disclosure:
[0051] Temperature shift precipitation techniques may also be used to form small particle dispersions. This technique is disclosed in U.S. Pat. No. 5,188,837, which is incorporated herein by reference and made a part hereof. In an embodiment of the invention, lipospheres are prepared by the steps of: (1) melting or dissolving a substance such as a drug to be delivered in a molten vehicle to form a liquid of the substance to be delivered; (2) adding a phospholipid along with an aqueous medium to the melted substance or vehicle at a temperature higher than the melting temperature of the substance or vehicle; (3) mixing the suspension at a temperature above the melting temperature of the vehicle until a homogenous fine preparation is obtained; and then (4) rapidly cooling the preparation to room temperature or below.

Description of Disclosure:
[0053] Reaction precipitation includes the steps of dissolving the pharmaceutical compound, and optionally other excipients, into a suitable solvent to form a solution. The compound may be added in an amount at or below the saturation point of the compound in the solvent. The compound or any of the excipients is precipitated from solution by reacting with a chemical agent or by modification in response to adding energy such as heat or UV light or the like such that the modified compound has a lower solubility in the solvent and precipitates from the solution to form a small particle dispersion. Precipitation of excipient provides a solid matrix into which the drug is sorbed.

Description of Disclosure:
[0059] There are numerous other methodologies for preparing small particle dispersions. The present invention provides a methodology for terminally sterilizing such dispersions without significantly impacting the efficacy of the preparation.

Description of Disclosure:
III. Additional Methods for Preparing Particle Dispersions of Pharmaceutical Compositions

Description of Disclosure:
[0061] The categories of processes are distinguished based upon the physical properties of the organic compound as determined through x-ray diffraction studies, differential scanning calorimetry (DSC) studies, or other suitable study conducted prior to the energy-addition step and after the energy-addition step. In the first process category, prior to the energy-addition step the organic compound in the presuspension takes an amorphous form, a semi-crystalline form or a supercooled liquid form and has an average effective particle size. After the energy-addition step the organic compound is in a crystalline form having an average effective particle size essentially the same or less than that of the presuspension.

Description of Disclosure:
[0062] In the second process category, prior to the energy-addition step the organic compound is in a crystalline form and has an average effective particle size. After the energy-addition step the organic compound is in a crystalline form having essentially the same average effective particle size as prior to the energy-addition step but the crystals after the energy-addition step are less likely to aggregate or form large crystals.

Description of Disclosure:
[0064] In the third process category, prior to the energy-addition step the organic compound is in a crystalline form that is friable and has an average effective particle size. What is meant by the term "friable" is that the particles are fragile and are more easily broken down into smaller particles. After the energy-addition step the organic compound is in a crystalline form having an average effective particle size smaller than the crystals of the pre-suspension. By taking the steps necessary to place the organic compound in a crystalline form that is friable, the subsequent energy-addition step can be carried out more quickly and efficiently when compared to an organic compound in a less friable crystalline morphology.

Description of Disclosure:
[0087] U.S. Pat. No. 5,780,062 discloses a process for preparing small particles of an organic compound by first dissolving the compound in a suitable water-miscible first solvent. A second solution is prepared by dissolving a polymer and an amphiphile in aqueous solvent. The first solution is then added to the second solution to form a precipitate that consists of the organic compound and a polymer-amphiphile complex. The '062 Patent does not disclose utilizing the energy-addition step of this process in Methods A and B. Lack of stability is typically evidenced by rapid aggregation and particle growth. In some instances, amorphous particles recrystallize as large crystals. Adding energy to the pre-suspension in the manner disclosed above typically affords particles that show decreased rates of particle aggregation and growth, as well as the absence of recrystallization upon product storage.

Description of Disclosure:
[0089] To this end, two formulations were prepared and analyzed. Each of the formulations has two solutions, a concentrate and an aqueous diluent, which are mixed together and then sonicated. The concentrate in each formulation has an organic compound (itraconazole), a water miscible solvent (N-methyl-2-pyrrolidinone or NMP) and possibly a polymer (poloxamer 188). The aqueous diluent has water, a tris buffer and possibly a polymer (poloxamer 188) and/or a surfactant (sodium deoxycholate). The average particle diameter of the organic particle is measured prior to sonication and after sonication.

Description of Disclosure:
[0092] Table 1 shows the average particle diameters measured by laser diffraction on three replicate suspension preparations. An initial size determination was made, after which the sample was sonicated for 1 minute. The size determination was then repeated. The large size reduction upon sonication of Method A was indicative of particle aggregation. TABLE-US-00001 TABLE 1 Average After particle diameter sonication Method Concentrate Aqueous Diluent (microns) (1 minute) A itraconazole (18%), N-methyl- poloxamer 188 18.7 2.36 2-pyrrolidinone (6 mL) (2.3%), sodium deoxycholate 10.7 2.46 (0.3%)tris buffer (5 mM, 12.1 1.93 pH 8)water (qs to 94 mL) B itraconazole (18%)poloxamer sodium deoxycholate 0.194 0.198 188 (37%)N-methyl-2- (0.3%)tris buffer (5 mM, 0.178 0.179 pyrrolidinone (6 mL) pH 8)water (qs to 94 mL) 0.181 0.177

Description of Disclosure:
[0093] A drug suspension resulting from application of the processes may be administered directly as an injectable solution, provided Water for Injection is used in formulation and an appropriate means for solution sterilization is applied. Sterilization may be accomplished by methods well known in the art such as steam or heat sterilization, gamma irradiation and the like. Other sterilization methods, especially for particles in which greater than 99% of the particles are less than 200 nm, would also include pre-filtration first through a 3.0 micron filter followed by filtration through a 0.45-micron particle filter, followed by steam or heat sterilization or sterile filtration through two redundant 0.2-micron membrane filters. Yet another means of sterilization is sterile filtration of the

concentrate prepared from the first solvent containing drug and optional surfactant or surfactants and sterile filtration of the aqueous diluent. These are then combined in a sterile mixing container, preferably in an isolated, sterile environment. Mixing, homogenization, and further processing of the suspension are then carried out under aseptic conditions.

Description of Disclosure:
[0097] The methods of the first process category generally include the step of dissolving the organic compound in a water miscible first solvent followed by the step of mixing this solution with an aqueous solvent to form a presuspension wherein the organic compound is in an amorphous form, a semicrystalline form or in a supercooled liquid form as determined by x-ray diffraction studies, DSC, light microscopy or other analytical techniques and has an average effective particle size within one of the effective particle size ranges set forth above. The mixing step is followed by an energy-addition step.

Description of Disclosure:
[0098] The methods of the second processes category include essentially the same steps as in the steps of the first processes category but differ in the following respect. An x-ray diffraction, DSC or other suitable analytical techniques of the presuspension shows the organic compound in a crystalline form and having an average effective particle size. The organic compound after the energy-addition step has essentially the same average effective particle size as prior to the energy-addition step but has less of a tendency to aggregate into larger particles when compared to that of the particles of the presuspension. Without being bound to a theory, it is believed the differences in the particle stability may be due to a reordering of the surfactant molecules at the solid-liquid interface.

Description of Disclosure:
[0099] The methods of the third category modify the first two steps of those of the first and second processes categories to ensure the organic compound in the presuspension is in a friable form having an average effective particle size (e.g., such as slender needles and thin plates). Friable particles can be formed by selecting suitable solvents, surfactants or combination of surfactants, the temperature of the individual solutions, the rate of mixing and rate of precipitation and the like. Friability may also be enhanced by the introduction of lattice defects (e.g., cleavage planes) during the steps of mixing the first solution with the aqueous solvent. This would arise by rapid crystallization such as that afforded in the precipitation step. In the energy-addition step these friable crystals are converted to crystals that are kinetically stabilized and having an average effective particle size smaller than those of the presuspension. Kinetically stabilized means particles have a reduced tendency to aggregate when compared to particles that are not kinetically stabilized. In such instance the energy-addition step results in a breaking up of the friable particles. By ensuring the particles of the presuspension are in a friable state, the organic compound can more easily and more quickly be prepared into a particle within the desired size ranges when compared to processing an organic compound where the steps have not been taken to render it in a friable form.

Description of Disclosure:
[0103] The seed compound can be precipitated from the first solution. This method includes the steps of adding the organic compound in sufficient quantity to exceed the solubility of the organic compound in the first solvent to create a supersaturated solution. The supersaturated solution is treated to precipitate the organic compound in the desired polymorphic form. Treating the supersaturated solution includes aging the solution for a time period until the formation of a crystal or crystals is observed to create a seeding mixture. It is also possible to add energy to the supersaturated solution to cause the organic compound to precipitate out of the solution in the desired polymorph. The energy can be added in a variety of ways including the energy addition steps described above. Further

energy can be added by heating, or by exposing the pre-suspension to electromagnetic energy, particle beam or electron beam sources. The electromagnetic energy includes light energy (ultraviolet, visible, or infrared) or coherent radiation such as that provided by a laser, microwave energy such as that provided by a maser (microwave amplification by stimulated emission of radiation), dynamic electromagnetic energy, or other radiation sources. It is further contemplated utilizing ultrasound, a static electric field, or a static magnetic field, or combinations of these, as the energy-addition source.

Description of Disclosure:
Preparation of an Indinavir Particle Suspension

Description of Disclosure:
[0107] An isotonic buffer solution was prepared by dissolving 1.8 grams of sodium chloride and 0.28 grams of sodium phosphate dibasic, in 200 mL water. 2.4 grams of Lipoid E80 was added to the buffer solution and dispersed, to make a homogenous dispersion. The pH of the dispersion was adjusted to 8.5. 1.2 grams of indinavir free base was added to the phospholipid dispersion and a pre-suspension was prepared using an Ultraturrax rotor-stator mixer for 4 minutes. The presuspension was then homogenized in a piston-gap homogenizer at 15,000 psi pressure for 40 passes. The final particle size mean of the suspension was 1.5 microns, with a D99 of 8.4 microns. The resulting composition ("Composition 1") is detailed in Table 2, below: TABLE-US-00002 TABLE 2 Composition 1: Indinavir Particulate Composition Ingredient Concentration (% w/v) Indinavir 0.6 Lipoid E80 1.2 Sodium chloride 0.9 Sodium Phosphate, Dibasic, Anhydrous 0.14 Sodium Hydroxide, NF/Hydrochloric pH 8.0 to 8.5 Acid, NF Sterile Water for Injection, USP Quantity Sufficient to 100%

Description of Disclosure:
[0108] Physical stability of the suspension was tested by measuring particle size at 2 weeks, 4 weeks, 3 months, and 6 months time intervals. Storage temperatures of 5.degree. C., 25.degree. C., and 40.degree. C. were tested. As can be seen in Table 5 the particle size mean increased slightly over the 6-months period, whereas the 99.sup.th percentile for the 5.degree. C. samples did not change significantly. TABLE-US-00003 TABLE 3 Long term stability data for Composition 1 Temp 5.degree. C. 25.degree. C. 40.degree. C. Time Mean 99% Mean 99% Mean 99% Weeks Microns Microns Microns 0 1.531 8.375 1.531 8.375 1.531 8.375 2 1.631 8.59 1.7165 7.452 1.757 8.539 4 1.6184 8.243 1.599 8.107 1.704 8.502 12 1.652 7.763 1.9521 8.078 1.9157 8.349 26 1.9173 8.043 nd nd nd Nd nd = Not determined

Description of Disclosure:
[0109] Compositions of the present invention comprising protease inhibitors can be prepared with carious surfactants and excipients and have various average effective particle sizes. Preferred compositions comprise indinavir particles coated with Lipoid E80 or other phospholipids and, optionally, an additional surfactant such as a non-ionic surfactant, e.g., the poloxamers including poloxamer 188. The surfactant concentrations in the compositions will vary, depending on need to maintain particle size range, but typically will be in an amount of from about 0.1 to about 10% w/v and more preferably from about 0.5 to about 2% w/v, of the composition. The particle size of the protease inhibitor particles will vary, but will typically be about 50 nm to about 5 microns, more preferably from about 100 nm to about 1.5 microns.

Description of Disclosure:
[0110] A preferred form of the invention involves a process for delivering a pharmaceutical composition to the tissue target of a mammalian subject. Each of the processes of this embodiment of the present invention include the steps of: (i) providing a dispersion of a pharmaceutically effective compound in particle form, (ii) contacting the dispersion with cells for cell uptake to form loaded cells, and (iii) administering the loaded cells for delivery tot he tissue target of a portion of the particles. The processes for drug delivery to the tissue target can be

divided into ex vivo and in vivo categories depending on whether the dispersion is contacted with the cells outside or inside the mammalian subject.

Description of Disclosure:
[0111] The ex vivo process includes the steps of: (i) isolating cells from the mammalian subject, (ii) contacting the cells with a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns, (iii) allowing sufficient time for cell uptake of a portion of the particles to form loaded cells, and (iv) administering to the mammalian subject the loaded cells to deliver a portion of the pharmaceutical composition to the tissue target. There are numerous types of cells in the mammalian subject that are capable of this type of cellular uptake and transport of particles. These cells include, but are not limited to, macrophages, monocytes, granulocytes, neutrophils, basophils, and eosinophils. Furthermore, particles in the size range of from about 150 nm to about 100 microns are more readily taken up by these phagocytic organisms.

Description of Disclosure:
[0112] Isolating macrophages from the mammalian subject can be performed by a cell separator. For instance, the Fenwal cell separator (Baxter Healthcare Corp., Deerfield, Ill.) can be used to isolate various cells. For example, a blood cell separator can be used for the attainment of a monocyte-enriched PBMC fraction isolation, and can also be used for the administration of such cells to the patient. Once isolated, the particulate pharmaceutical composition is contacted with the isolated cell sample and incubated for short period of time to allow for cell uptake of the particles. Up to an hour can be given to permit sufficient cell uptake of the drug particles. Uptake by the cells of the dispersion of the pharmaceutical composition as particles may include phagocytosis or adsorption of the particle onto the surface of the cells. Furthermore, in a preferred form of the invention, the particles during contact with the cells are at a concentration higher than the thermodynamic saturation solubility thereby allowing the particles to remain in particulate form during uptake and delivery to the brain by the cells. For marginally soluble drugs, e.g. indinavir, the ex-vivo procedure can be utilized provided that the isolated cells are able to phagocytize the pharmaceutical composition particles at a faster rate than the competing dissolution process. The particles should be large enough to allow for the cells to phagocytize the particles and deliver them to the brain before complete dissolution of the particle. Furthermore, the concentration of the pharmaceutical composition should be kept higher than the saturation solubility of the composition so that the particle is able to remain in the crystalline state during phagocytosis.

Description of Disclosure:
[0116] In another preferred embodiment, the pharmaceutical composition as particles is administered directly into the vascular system of a mammalian subject. The particles can be engulfed by phagocytic cells residing in the vascular system or adsorbed onto the cell wall. Once the particle is taken up by the loaded cell, a certain percentage of the loaded cells will be transported across the blood-brain barrier into the brain in a manner similar to transport across the cerebrospinal fluid-brain barrier.

Description of Disclosure:
[0118] Another preferred embodiment of this invention is a pharmaceutical composition for delivery to the brain of a mammalian subject. Suitable compositions are in the form of a dispersion of the pharmaceutical composition provided as particles having an average particle size of from about 150 nm to about 100 microns and adapted for administering to a mammalian subject for delivery to the brain of an effective amount of the pharmaceutical composition by cells capable of reaching the brain.

CLAIMS:

1. A method for delivering a pharmaceutical composition to a tissue target of a mammalian subject, the method comprising the steps of: (i) providing a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns; and (ii) administering the dispersion to the mammalian subject for delivery to the brain of a portion of the pharmaceutical composition by cells capable of reaching the brain.

8. A composition for delivery to a brain of a mammalian subject comprising a dispersion of a pharmaceutical composition provided as particles having an average particle size of from about 150 nm to about 100 microns and adapted for administering to the mammalian subject for delivery to the brain of an effective amount of the pharmaceutical composition by cells capable of reaching the brain.

20. A method for delivering a pharmaceutical composition to a tissue target of a mammalian subject, the method comprising the steps of: (i) isolating cells from the mammalian subject; (ii) contacting the cells with a dispersion of the pharmaceutical composition as particles having an average particle size of from about 150 nm to about 100 microns; (iii) allowing for cell uptake of a portion of the particles to form loaded cells; and (iv) administering to the mammalian subject the loaded cells to deliver a portion of the pharmaceutical composition to the tissue target.

27. A method of treating a patient having a central nervous system with HIV by delivering an anti-HIV composition to a brain of the patient, the method comprising the steps of: (i) providing a dispersion of the anti-HIV composition as particles having an average particle size of from about 150 nm to about 100 microns; and (ii) administering to the central nervous system of the patient the dispersion for delivery of a portion of the anti-HIV composition by macrophages to the brain.

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L3: Entry 34 of 93 File: PGPB May 22, 2003

DOCUMENT-IDENTIFIER: US 20030096013 A1
TITLE: Preparation of submicron sized particles with polymorph control

Detail Description Paragraph:
[0059] One suitable emulsion precipitation technique is disclosed in the co-pending and commonly assigned U.S. Ser. No. 09/964,273, which is incorporated herein by reference and is made a part hereof. In this approach, the process includes the steps of: (1) providing a multiphase system having an organic phase and an aqueous phase, the organic phase having a pharmaceutically effective compound therein; and (2) sonicating the system to evaporate a portion of the organic phase to cause precipitation of the compound in the aqueous phase and having an average effective particle size of less than about 2.mu.m. The step of providing a multiphase system includes the steps of: (1) mixing a water immiscible solvent with the pharmaceutically effective compound to define an organic solution, (2) preparing an aqueous based solution with one or more surface active compounds, and (3) mixing the organic solution with the aqueous solution to form the multiphase system. The step of mixing the organic phase and the aqueous phase can include the use of piston gap homogenizers, colloidal mills, high speed stirring equipment, extrusion equipment, manual agitation or shaking equipment, microfluidizer, or other equipment or techniques for providing high shear conditions. The crude emulsion will have oil droplets in the water of a size of approximately less than 1 .mu.m in diameter. The crude emulsion is sonicated to define a microemulsion and eventually to define a submicron sized particle suspension.

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L3: Entry 71 of 93 File: USPT Jul 27, 1993

DOCUMENT-IDENTIFIER: US 5231112 A
TITLE: Compositions containing tris salt of cholesterol hemisuccinate and antifungal

Detailed Description Text (172):
(c) .sup.51 Cr in EPC-SPLVs were prepared by the general procedure described in detail in copending application Ser. No. 476,496, filed Mar. 24, 1983 and now U.S. Pat. No. 4,522,803 by Lenk et al. entitled "Stable Plurilamellar Vesicles, Their Preparation and Use", which is incorporated by reference herein. To this end, 5 ml batches were prepared by dissolving 65 mg egg phosphatidylcholine (EPC) in chloroform and drying down the EPC to form a film. The film was resuspended in 10 ml ether and 0.3 ml .sup.51 CrO.sub.2.sup.= in 0.9% saline (pH 8) was added. The mixture was then emulsified by sonication while concurrently evaporating the ether under N.sub.2 gas. The resulting stable plurilamellar vesicles (SPLVs) were resuspended in 5 ml 0.01M Tris-HCl, pH 7.3, 0.14M NaCl, 5% dextrose and pelleted by centrifugation. The pellet was washed three times to remove unentrapped .sup.51 Chromium and the final pellet was resuspended in 5 ml 0.01M Tris-HCl, pH 7.3, 0.14M NaCl, 5% dextrose. The final concentration of EPC was 13 mg/ml. Twelve 40 g male Swiss Webster mice each received a 0.1 ml (about 100,000 cpm) intravenous injection via the tail vein.

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L3: Entry 87 of 93 File: USPT May 13, 1986

DOCUMENT-IDENTIFIER: US 4588578 A
TITLE: Lipid vesicles prepared in a monophase

CLAIMS:

2. The method according to claim 1 in which the monophase is sonicated during evaporation.

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